EDITORIALS

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Research: Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes (*BMJ* 2013;346:f1169)
Editorial: Vitamin D: some perspective please (*BMJ* 2012;345:e4695)
Research news: Vitamin D supplementation to prevent osteoporosis is not warranted, study concludes (*BMJ* 2013;347:f615)

Vitamin D and chronic disease prevention

Multiple meta-analyses don't support a role as magic bullet

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Vitamin D "deficiency" (circulating 25-hydroxyvitamin D concentration <30 nmol/L) has been linked to a remarkable array of chronic diseases, including bone mineral disease, autoimmunity, cancer, diabetes, and cardiovascular outcomes.[1] So plentiful are vitamin D's putative mechanistic actions that it has been whimsically invoked as an explanation for why good triumphs over evil in *The Hobbit*.[2] Parody aside, the vitamin D literature comprises a minefield of observational data and mixed quality evidence from mostly small trials. Interpretation of the data is further muddied by seemingly endless media reports suggesting vitamin D as a panacea for chronic disease.[3 4]

Against this backdrop, two new papers bravely attempt to make sense of the existing data. Theodoratou and colleagues (p 11) highlight differences between observational data (relating circulating 25-hydroxyvitamin D to outcomes) and randomised controlled trials of supplementation.[5] Of a remarkable 137 different outcomes reportedly linked to 25-hydroxyvitamin D, only 10 had also been tested in trials, and only one (birth weight) had apparently concordant evidence of "benefit" from observational studies and trials. This pattern of findings should ring alarm bells; observational epidemiology extolled the virtues of antioxidant vitamins, only for major trials of vitamins E and C and β carotene to show null, or even some harmful, effects of supplementation on a range of outcomes.[6-8]

Beware confounding and reverse causality

This highlights the problems of confounding and reverse causality that can lead to premature causal inferences in observational studies.[9] Such factors are even more applicable to vitamin D; circulating concentrations can be lowered not only by lack of sun exposure but also by inflammation, smoking, obesity, and poor diet.[10-12] Consequently, observational data linking 25-hydroxyvitamin D concentrations to any outcome can only ever be hypothesis generating.

Taking a different approach, Chowdhury and colleagues (p 12) provide a new meta-analysis of observational and trial data relating vitamin D (given alone as either the D_2 or D_3 preparation), to risk of all cause mortality.[13] Their observational analyses unsurprisingly confirmed low 25-hydroxyvitamin D to be associated with elevated risk of multiple adverse outcomes. However, their analysis of trials provides the most noteworthy finding: whereas D_2 supplementation did not seem to reduce all cause mortality (relative risk 1.04, 95% confidence interval 0.97 to 1.11), D_3 supplementation did (0.89, 0.80 to 0.99). A previous Cochrane review also reported a reduction in all cause mortality with the use of D_3, albeit of lower magnitude (relative risk 0.94, 0.91 to 0.98).[14]

The apparent degree of benefit from D_3 in the new analyses—11% lower mortality—seems remarkable, but before these results are taken as a green light for widespread D_3 supplementation, several limitations must be considered. Firstly, 14 trials contributed to the D_3 meta-analysis, totalling only 13 637 participants, and six of these were scored as being at high risk of bias. Contrast this to meta-analyses of large scale antihypertensive and statin trials,[15 16] which have an order of magnitude more participants, generally in better quality studies. Secondly, indicative of inherent uncertainty, different authors have reached somewhat differing conclusions despite exhaustive analysis on apparently overlapping datasets.[5 14 17]

Thirdly, the four studies (n=10 197) that contributed the most power to the D_3 trial meta-analyses were conducted in older people and had fractures as the primary outcome. If we accept a small benefit of vitamin D supplementation on risk of fracture, although even this has been challenged,[5 17 18] the observed reduction in mortality may have been secondary to avoidance of in-hospital complications and loss of independence in later life. Any potential reduction in mortality may therefore not be generalisable to middle aged populations. Finally, and perhaps most importantly, vitamin D supplementation may not be without harm. Theodoratou and colleagues highlight an increased risk of hypercalcaemia in chronic kidney disease,[5] a side effect that can also occur in people without renal disease.[19 20] Thus, larger studies are still needed to rule out potential adverse effects.

We suggest three take home messages from these two new studies. Firstly, healthcare professionals should treat all observational data cautiously, as existing disease and associated risk factors may cause, rather than be a consequence of, low circulating 25-hydroxyvitamin D. Secondly, before widespread supplementation can be considered, new trial data are needed with a focus on potential risks as well as benefits; further reanalysis of existing data will not suffice. Fortunately, new trials are under way—for example, VITAL,[21] which has recruited 26 000 men and women and randomised them to 2000 IU D_3, omega-3 fatty acid, or placebo in a two by two factorial design. Its primary outcomes will be cancer, coronary heart disease, and stroke, and it is due to report around 2017. This study alone will therefore substantially increase the available D_3 trial evidence base, and, importantly, extend it to younger people.

Finally, while we wait for results of major trials, clinicians should avoid costly measurement of 25-hydroxyvitamin D in asymptomatic patients outside of bone disease related conditions.[22] Some may argue that supplementing those who are apparently "deficient" is cheap, but patients may gain false reassurance from prescription of a "protective" tablet. To improve health and prevent chronic disease, we should stick to what is proven: encourage better lifestyles in general and target established risk factors in people at elevated risk.

Competing interests and references are in the version on bmj.com.

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RESEARCH, pp 11, 12

A better idea than supplements

bmj.com
- Clinical review: Management of infantile colic (*BMJ* 2013;347:f4102)
- Research news: Migraine in childhood linked to colic in infancy (*BMJ* 2013;346:f2419)
- Editorial: Probiotic supplements (*BMJ* 2013;347:f713)

Probiotics and infant colic

Still a hammer in search of a nail

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In a linked paper, Sung and colleagues (p 14) describe a large, randomised, placebo controlled trial of *Lactobacillus reuteri* for the management of infant colic.[1] This represents the most definitive and well designed study to date on this controversial topic.

Infant colic is a challenging problem for many parents, but the cause and effective treatment remain elusive. As its name suggests, colic was thought to arise in the gastrointestinal tract, but after centuries of this supposition we still do not know if it is true. A host of home remedies and drug treatments have circulated over the years, ranging from whisky, to acid suppression, to anticholinergic agents, and onwards to medicine's most recent "hammer looking for a nail," probiotics.

Sung and colleagues used a well defined case definition (the Wessell criteria), and enrolled patients at urgent care centres who met these criteria. In total, 167 infants were randomised to *L reuteri* or placebo. At multiple follow-up intervals, the authors found no improvement in the duration of crying time in infants who received probiotic compared with placebo (in fact, infants receiving probiotic cried significantly more). The authors also assessed secondary outcomes, including measures of maternal mental health, family functioning, and family quality of life, none of which differed between arms.

In contrast, last month Indrio and colleagues published the results of a multi-institutional trial.[2] They found that prophylactic probiotic use for the first three months of life in normal newborns reduced the number of parent reported crying times compared with placebo (mean 71 *v* 38 minutes a day at 3 months). Additionally, the frequency of regurgitation and bowel movements was also "improved," although defining these quantities as disease states is often specious in infants.

Unfortunately, these two large studies—both of which constitute the best evidence to date—assessed two different clinical scenarios. Indrio and colleagues sought to answer the question: "Should we give probiotics to all infants to help prevent fussiness/colic?," whereas Sung and colleagues asked: "Should we give probiotics to infants with colic to improve their symptoms?"

Taking the wrong road

Fifty years ago, paediatrician Morris Green coined the term "the vulnerable child syndrome" to describe the far reaching family effects of a perceived threat to a child's life.[3] Since then many investigators have studied the effects of labelling a child as ill. Tarini and colleagues have shown that labelling a normal, benign process as a disease (such as infant regurgitation) has a substantial impact on parents' expectations for treatment, even if they are informed that the treatment is ineffective.[4] This process has resulted in hundreds of thousands of prescriptions for acid suppressants in infants over the past decade, despite evidence that their use increases the risk of respiratory and gastrointestinal infections.[5] We should be careful not to walk this same road with probiotics and colic.

Furthermore, we know little about the acquisition and development of the microbiota in an infant's gut. We are far from a sufficiently thorough understanding that would allow us to link changes in specific bacterial populations to changes in infant behaviour, given the enormous variation and complexity of both behaviour and microbiome composition between and among individuals. For instance, some investigators have described higher levels of faecal calprotectin (an inflammatory marker) in colicky infants,[6] whereas others have found equally high levels in healthy, asymptomatic breastfed infants.[7] This all points to our strikingly poor understanding of the normal intestinal milieu in infants, so we should hesitate to proclaim victory over colic just yet, or to aggressively alter the development of intestinal microbiota without a better understanding of normal intestinal development.

Await the tincture of time

Some recent studies have shown an association between colic and the later development of functional disorders such as migraine.[8] Some investigators cite this fact as justification for drug intervention for colic, under the auspices of preventing these later problems. This is a fallacious path. Functional disorders, especially those heavily influenced by social environment and parental perception, will naturally cluster together, and to suppose that early treatment of colic will somehow prevent children from developing functional pain disorders is an oversimplification of a complex set of disorders.

Amid this sea of conflicting evidence, what does work? Nearly all studies evaluating treatments for infant colic have methodological shortcomings or conflicting results. Probiotics have been studied most rigorously and results have been mixed.[9] Simethicone and acid suppression have been convincingly shown to be ineffective.[10] Dicycloverine (dicyclomine) and cimetroprium have marginal effectiveness but also have potentially worrying side effects.[11] Maternal dietary changes or hydrolysed infant formulas are poorly evaluated, but some studies report positive results.[12 13]

So, with such a dearth of good evidence, perhaps the more important question is: "Should we be treating infant colic at all?" A great deal of accumulated clinical experience tells us that children with colic incur no serious long term effects from the disorder, and that symptoms abate with time. The potential harm associated with diagnostic testing and treatment of infants is likely to surpass the harm from colic itself.

For us to continue to perform drug intervention trials for this problem perhaps underscores our unwillingness to accept that colic is likely to represent a heterogeneous disorder with many complex inputs. As the old adage goes, "babies cry." Parents and their babies may be better served if we devote more resources to studying the interventions recommended long before the discovery of probiotics: reassurance, family social support, and the tincture of time.

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RESEARCH, p 14

Last year, the committee said that, even if the vaccine were free, the cost of programme implementation and adverse events would outweigh any protection

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News: Meningitis B vaccine to be introduced in UK after U turn on its cost effectiveness (*BMJ* 2014;348:g232)

Introducing a new group B meningococcus vaccine

Many forces affect the final decision

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The introduction of a new vaccine is highly complex, particularly a new category of vaccine with no biological precedent. The new group B meningococcus vaccine Bexsero (4CMenB),[1] developed using a genomic based reverse vaccinology approach,[2] is a case in point. When a vaccine is targeted against a relatively common disease, the company usually sponsors a large randomised controlled trial to show that the vaccine works. Group B meningococcal infection is sufficiently rare, however, that such a trial is not feasible.

In most countries, advice on vaccines and immunisation programmes is given to governments by independent committees. This advice includes data on vaccine effectiveness, the likelihood that the vaccine will confer herd immunity, safety, and cost effectiveness. In the United Kingdom, the Joint Committee on Vaccination and Immunisation (JCVI) has such a role. In the UK,[3] and in Australia, Canada, the United States, and many European countries, the government is not permitted in law to fund an immunisation programme unless its advisory committee says it is cost effective.

Different countries allow different assumptions in the modelling, so they do not always reach the same decision. The process usefully distances the government from the decision, which is made on scientific and economic grounds. Decisions are made on quality adjusted life years (QALYs), but this does not account for the politics.[4] Health economists ask what health benefit we get from buying a vaccine. Politicians may want to buy votes as well and are fearful of losing them if they do not bow to pressure. Pressure comes from patient groups and doctors, who understandably advocate for their patients. Drug companies know the power of such advocacy and are increasingly adept at stoking the fire using advertising agencies and media campaigns. This may distort the decision making process in such a complex area.

4CMenB was considered by the JCVI, which used data on immunogenicity and possible herd immunity to model the likely extent of protection.

JASON LEE/REUTERS/CORBIS

How much is too much?

In July 2013, the committee published an interim statement advising that 4CMenB "would not be cost effective in an infant immunisation schedule at any price."[5] This was a surprisingly strong statement: the committee said that, even if the vaccine were free, the cost of programme implementation and adverse events would outweigh any protection.

After an outcry,[6] the committee considered new data—including modelling data and litigation costs for cases of meningococcal infection—and revised its decision.[1 7] In March 2014, the committee recommended a three dose infant programme if a cost effective price could be agreed."[7] The UK government then announced that the infant group B meningococcal vaccination programme would go ahead if a cost effective price could be agreed.

Predictably, the press announced the decision as if it were definite.[8] This must surely put extra pressure on the Department of Health when it negotiates the vaccine price with Novartis. Although transparency is laudable, the department might have reduced this pressure by delaying the announcement until a cost effective vaccine price had, or had not, been reached.

The introduction of 4CMenB vaccine in the UK would be beneficial and would inform the rest of the world about the true value of this new vaccine. The UK was the first country to pay for a group C meningococcal vaccine, a decision that was vindicated by finding that the vaccine was not only effective, but prevented infections in unimmunised people, and without serogroup replacement.[9] Children and adults in many other countries benefited from the data. However, the group C meningococcal vaccine is a conjugate vaccine, so there was prior proof of principle of action based on experience with the *Haemophilus influenzae* type b and pneumococcal vaccines. On the basis of projections of group B meningococcus coverage alone, it is highly unlikely that the 4CMenB vaccine will be nearly as effective. Even if vaccine efficacy is low, however, withdrawal of an established group B meningococcal vaccination programme would be difficult.

Does it really matter if the UK government pays too much for 4CMenB? There are some potential serious harms. Firstly, if governments bow to societal and corporate pressure, the benefit of maintaining the separation between science and state is undermined. The situation with expensive vaccines also applies to orphan drugs,[10] particularly those for cancer. The UK has already established a special cancer fund that spends £200m (€240m; $331m) annually to buy cost ineffective anti-cancer drugs.[11] Although the UK press has suggested conspiracy, the government and the JCVI strongly deny any government interference with the advisory process regarding 4CMenB.

Our era of vaccine hesitancy

Secondly, vaccines are given to a large number of people, so even if a small proportion experience adverse effects, the absolute number affected may be large. We live in an era of vaccine hesitancy and are intolerant of risk. The decision to move from whole cell pertussis vaccines to acellular ones, made on the basis of the reactogenicity of whole cell vaccines and limited data about duration of protection, is being called into question given concerns of reduced vaccine effectiveness.[12] Pertussis refuses to go away and infants still die from it despite high coverage.[12]

New vaccines need to be safe if we are to sustain public trust.[13] 4CMenB is a reactogenic vaccine with high rates of fever, and an increase in febrile convulsions is possible. If the vaccine causes measurable harms but its efficacy is low or uncertain, the public pressure for the vaccine may turn all too quickly to condemnation for putting so many children at risk. Immunisation programmes are sustainable only as long as the public trusts the vaccine involved.

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Sihvonen and colleagues study provides good evidence to challenge the indiscriminate selection of patients for arthroscopic meniscectomy

Arthroscopy for degenerate meniscal tears of the knee

Not all patients with non-traumatic tears and medial joint pain require meniscectomy

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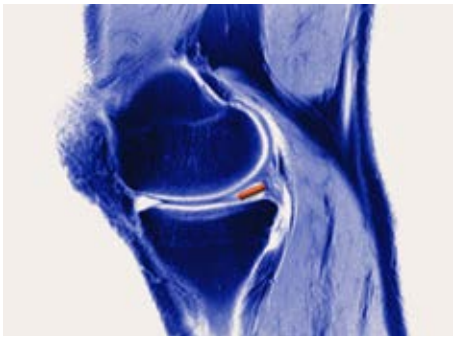
The NHS performs around 150 000 arthroscopic knee operations a year, with more than half involving resection of the meniscus. Therefore, close scrutiny of this intervention in the United Kingdom is entirely appropriate, particularly in the context of the ongoing drive towards providing evidence based and value based care.

Considering such high rates of surgery, it would be natural to assume that this operation is backed up by adequate evidence. However, unlike knee replacement surgery, which is supported by population based patient reported outcomes (PROMs) data and the National Joint Registry, healthcare commissioners lack the necessary data to allow informed decision making for knee arthroscopy. Detailed indications for its use need further refinement. With this backdrop, any results from high quality randomised controlled trials in this area are welcome.

The recent study by Sihvonen and colleagues therefore makes interesting reading.[1] In 2005, when the trial was started, investigators were worried about the increasing numbers of arthroscopic meniscectomies performed for patients with degenerative meniscal tears. At this time it was common practice to perform arthroscopy on patients with a history of joint line pain in the presence of an isolated degenerative meniscal tear. These inclusion criteria were therefore used for a sham surgery trial that investigated the efficacy of arthroscopy. The researchers found no difference in outcome between actual and sham surgery and concluded that the practice of resection for degenerative meniscal tears should be challenged, if not discontinued.

Their study provides good evidence to challenge the indiscriminate selection of patients for arthroscopic meniscectomy, and fewer patients will probably undergo surgery for this indication in future. In addition, the researchers are to be commended on completing a placebo controlled trial of surgery. Unlike drug trials, randomised trials of surgical interventions are rare. The addition of a sham or placebo, commonplace in drug trials, is rare in surgical trials and adds a further layer of complexity.



LIVING ART ENTERPRISES/SPL

Question of efficacy in subgroups remains

But does the study completely answer the question of whether degenerate tears should be resected? Perhaps not. Closer inspection identifies some methodological problems that may influence interpretation.

The trial began in 2005 and was designed before this. The long duration of the trial is important because it affects the external validity and generalisability of the findings. Generalisability is a key requirement for an assessment of the impact on healthcare systems. Trials that investigate outdated or non-contemporary interventions seldom have any effect.

Whether the treatment used in the trial represents current practice is questionable, with the standard approach for this population having moved on since the trial's inception. In general, the identification of candidates for arthroscopic surgery is now more sophisticated, with some subgroups potentially more suitable for meniscectomy than others. For example, patients who sustain a traumatic cartilage tear that results in mechanical symptoms (catching or locking) may benefit from arthroscopy.[2] Similarly, a further subset of patients with degenerative tears, initially managed non-operatively, may have recurring symptoms over a longer period, as seen in recent crossover trials of arthroscopic meniscectomy in other groups.[3 4] For this patient group, where discrete unstable meniscal fragments are identified on magnetic resonance imaging, meniscectomy may also be an effective treatment. Further trials are needed to evaluate the worth of arthroscopy in these distinct and separate populations.

The work also highlights some interesting problems in the design of placebo controlled surgical trials. In this study the placebo or sham procedure involved a joint washout. Sceptics will claim that joint washout is not an inert intervention and may have a therapeutic element (despite the much cited sham surgery study of Moseley and colleagues, which showed a lack of efficacy for arthroscopic washout).[5] The inclusion of a washout for both groups makes interpretation of the trial more difficult. Although meniscal resection seems to provide little extra benefit over arthroscopic washout, only a third "no treatment" group could delineate the effects of a washout only.

Washout

A more appropriate conclusion for this study might have been that arthroscopic meniscectomy (for degenerative tears) offers no more benefit than washout alone. This is very different from stating that arthroscopy is ineffective—one of the messages publicised in the media.[6] Through no fault of the authors, the media and deliberate troublemakers might exploit a sensational headline and use this research to condemn arthroscopy for all populations. Our objective in raising these issues is not to criticise laudable efforts, but to caution against the propagation of selective or erroneous interpretations. Every worthwhile randomised controlled trial should be given the chance to influence clinical practice in an appropriate manner.

Sihvonen and colleagues' study is a good example of the progress made in introducing rigorous and inventive methods to surgical trials. The work provides some valuable information about the indications for knee arthroscopy that will hopefully guide a change in practice, perhaps reducing the numbers of unnecessary procedures performed. At the same time, the work reinforces the urgent need for the orthopaedic community to confirm the potential, and often assumed, efficacy of meniscectomy in other patient subgroups.

This type of research is pivotal to the creation of evidence based surgical practice. We need sensible interpretation of well constructed trials to provide the necessary support for all effective surgical interventions (new or established), but equally to challenge the practice of ineffective surgery.

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